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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/445,865	02/11/2000	PHILIP JOHN BURKE	ERD100	1461

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EXAMINER	
NICKOL, GARY B	

ART UNIT	PAPER NUMBER
1642	23

DATE MAILED: 12/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/445,865	BURKE ET AL.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29,31-33,40 and 41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29,31-33 and 40* is/are rejected.

7)☒ Claim(s) *41* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

In view of the Appeal Brief filed on August 28, 2002, PROSECUTION IS HEREBY REOPENED. New grounds of rejections are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

Claims 29, 31-33, and 40-41 are pending. (Claims 1-28, 30, and 34-39 were cancelled in Paper No. 11)

All previous rejections are withdrawn in view of applicant's arguments filed in the Appeal Brief. This is a non-final action.

Information Disclosure Statement

The information disclosure statements (Paper Nos. 6, 10, and 13) have been considered as each reference was properly filed with the Office. A copy with the Examiner's signature is attached with this Action.

Claim Objections

Claim 33 is objected to for reciting "the prodrug **or** NRH" because the method from which Claim 33 depends from (claim 29) is not in the alternative- with regards to administering the prodrug and NRH. Both the prodrug *and* NRH are administered. Hence, the determining step of Claim 33 must be prior to administering the "prodrug *and* NRH or an analogue therof".

Claim 41 objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 29, 31-33 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Friedlos *et al.* (Biochem. Pharmacol. 44(9) pages 1739-43, 1992, IDS) in view of Jaiswal, A. (J.Biol.Chem. 269(20), pages 14502-08, 1994, IDS)

The claims are drawn to a method of treating a human patient with a target cell to be destroyed wherein the target cell expresses NQO2 the method comprising administering to a patient a prodrug which is converted to a cytotoxic drug by the action of NQO2 and nicotinamide riboside (reduced) (NRH) or an analogue thereof which can pass reducing equivalents to NQO2, wherein the prodrug is CB1954 (Claim 29); wherein the analogue of NRH is able to permeate the target cell membrane (Claim 31); wherein the target cell is a tumor (Claim 32); the method of claim 29 further comprising determining, before administering the prodrug or NRH or an analogue thereof, whether the target cell to be treated expresses NQO2 (Claim 33); wherein the patient has cancer (Claim 40).

Friedlos *et al.* teach a method of treating a human target cell to be destroyed (MAWI-human colon carcinoma, see Materials & Methods, page 1739) comprising administering CB1954 and nicotinamide riboside (reduced) (NRH) or an analogue thereof (NADH) which is able to permeate the target cell membrane. Friedlos *et al.* further teach that CB1954 is an exceptionally potent anti-tumor agent in-vivo capable of curing the rat Walker 256 carcinoma (1st paragraph, line 1), but CB-1954 has not been successful for the treatment of human tumors

(page 1739, 2nd paragraph). However, Friedlos *et al.* teach (page 1743, last paragrah) that the lack of success of CB 1954 as an anti-tumor agent in humans is because of the relative inactivity of human DT diaphorase (NQO1) towards CB1954, however such inactivity can be overcome by the addition of NADH resulting in enhanced cytotoxicty of CB1954 (see abstract also).

Friedlos *et al.* do not specifically teach treating a human patient with cancer nor do they characterize the target cell to be destroyed as expressing NQO2.

Jaisawl teaches that that the protein encoded by the NQO2 gene catalyzes 4-nitroreduction of the anti-tumor compound CB10-200 with almost "equal efficiency" as the NQO1 protein (page 14502, 2nd column, last paragraph). Jaiswal further teaches CB10-200 is an analog of nitrophenylaziridine (page 14503, 2nd column, 2nd paragraph). Since CB1954 is also known as "dinitrophenylaziridine", such substrates (CB1954 and CB10-200) are essentially members of the same family of anti-tumor agents. Jaiswal further teaches that CNQO1 is expressed in all tissues and that NQO2 is expressed in several human tissues including heart, lung, liver, skeletal muscle, kidney and pancreas (page 14502, 2nd column, last paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modulate the method of Friedlos *et al.* so as to administer to a human patient with cancer the prodrug CB1954 and nicotinamide riboside (reduced) (NRH). One would have been motivated to do so because Friedlos *et al.* teach that the lack of success of CB 1954 as an anti-tumor agent in humans is because of the relative inactivity of human DT diaphorase (NQO1) towards CB1954, however such inactivity *can be overcome* by the addition of NADH resulting in enhanced cytotoxicty of CB1954. Thus, since it is well known in the art that CB-1954 is a potent anti-tumor agent in-vivo capable of curing the rate Walker 256 carcinoma via

the activity of NQO1 converting the drug to a cytotoxic form, one would have a reasonable expectation that the pro-drug would also be converted into a cytotoxic form in a human patient since Friedlos *et al.* have shown that the relative inactivity of human DT diaphorase (NQO1) towards CB1954 *can be overcome* by the addition of NADH or NRH in human tumor cells in-vitro. Further, although Friedlos *et al.* do not characterize the target cells as expressing NQO2, any administration of the claimed compounds would anticipate target cells to be destroyed as expressing NQO2 since it was well known in the art at the time the invention was made that NQO2 was expressed in several human tissues including heart, lung, liver, skeletal muscle, kidney, and pancreas. Moreover, since Jaisawl teaches that the protein encoded by the NQO2 gene catalyzes 4-nitroreduction of the anti-tumor compound CB10-200 with almost "equal efficiency" as the NQO1 protein, and since CB10-200 and CB1954 are nitrophenylaziridine analogs, i.e. members of the same family of anti-tumor agents, it would have been obvious to one of ordinary skill to determine whether or not such target cells expressed NQO2 (or NQO1) prior to the administration of the prodrug and NRH or an analogue thereof because such a determination would obviously enhance the efficacy of the treatment. In other words, if the target cells did not express NQO2 or NQO1, it would be obvious to one of skill in the art that such an administration would not effectively destroy the target cell.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
November 25, 2002